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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: :
MOHIUDDIN ET AL. :
Serial No.: 330,156 : Group Art Unit: 336
Filed: March 29, 1989 : Examiner: M. POLUTTA
For: NOVEL METHOD OF : Attorney Docket No.:
MYOCARDIAL IMAGING : 7253-003

INFORMATION DISCLOSURE STATEMENT
UNDER 37 C.F.R. §1.56

Honorable Commissioner of Patents and Trademarks,
Washington, D.C. 20231

Sir:

In accordance with Applicants' continuing obligation to bring to the attention of the Patent Office all references coming to their attention which are or may be related to the examination of the invention of the subject application, Applicants hereby direct the Examiner's attention to the following references, copies of which are being submitted herewith.

LIST OF CITED REFERENCES

1. Strauss et al., American Journal of Cardiology, Vol. 39, pp. 403-406 (1977).
2. Rumberger et al., Journal of the American College of Cardiology, Vol. 9, no. 1, pp. 59-69 (1987).
3. McCall et al., Canadian Journal of Cardiology, Vol. 2, no. 3, pp. 176-183 (1986).
4. Biaggioni et al., Life Sciences, Vol. 39, pp. 2229-2236 (1986).
5. Hellmann et al., American Journal of Physiology, Vol. 231, no. 5, pp. 1495-1500 (1976).
6. Watt et al., British Journal of Clinical Pharmacology, 24: pp. 665-668 (1987).

7. Wilson et al., Circulation, Vol. 82, no. 5, pp. 1595-1606 (1990).
8. Zijlstra et al., Catheterization and Cardiovascular Diagnosis, 15: pp. 76-80 (1988).
9. Pantely et al., Circulation, Vol. 82: pp. 1854-1856 (1990).
10. U.S. Patent No. 4,880,783.
11. PCT International Application No. SE85/00423; International Publication No. WO87/01593.
12. PCT International Application No. SE83/00003; International Publication No. WO83/02391.

EXPLANATION OF RELEVANCE OF LISTED REFERENCES

1. Reference (1) by Strauss et al. is entitled "Noninvasive Detection of Subcritical Coronary Arterial Narrowing with a Coronary Vasodilator and Myocardial Perfusion Imaging". This reference was cited in the European Search Report issued for the present applications European counterpart. The reference discloses experiments performed on anesthetized dogs utilizing ethyl adenosine-5-carboxylate and myocardial perfusion imaging wherein the radiopharmaceutical agent used was thallium-201. The experiments involved snaring a small segment of the anesthetized dog's left circumflex coronary artery, in order to, as the authors allege, create an artificial subcritical coronary stenosis. Thereafter, the anesthetized dogs were administered ethyl adenosine-5-carboxylate intravenously in a bolus dose of 1 mg/kg. Thallium-201 was then administered to the anesthetized dog and myocardial perfusion imaging was performed on the dog in order to determine myocardial blood

perfusion. The author states that based on this imaging, there was a decrease in tracer concentration in the zone of the left ventricular supplied by snared left circumflex coronary artery.

2. Reference (2) by Rumberger et al. is entitled "Use of Ultrafast Computed Tomography to Quantitate Regional Myocardial Perfusion: A Preliminary Report". This reference was cited in the European Search Report issued for the present applications European counterpart. The reference discloses experiments performed in anesthetized dogs to quantify regional myocardial perfusion utilizing adenosine, radiolabelled microspheres and rapid acquisition computed axial tomography. There is no mention that the anesthetized dogs used in this study had coronary artery disease. The reference states that independent myocardial perfusion measurements were obtained by coincident injection of radiolabelled microspheres into the left atrium during control, intermediate and maximal myocardial vasodilation with adenosine.

3. Reference (3) by McCall et al. is entitled "Effect of Ischemia-Related Metabolic Factors on Thallium Exchange in Cultured Rat Myocardial Cells". This reference was cited in the European Search Report issued for the present applications European counterpart. The reference discusses the influence of various interventions designed to simulate the metabolic consequences of ischemia on thallium-204 uptake and release in cultured rat myocardial cells. One of these interventions involved the addition of adenine nucleosides, adenosine, inosine and hypoxanthine, to the

incubating solution of myocardial cells. The reference states that this had no effect on thallium influx or efflux in the cells.

4. Reference (4) by Biaggioni et al. is entitled "Cardiovascular Effects of Adenosine Infusion in Man and Their Modulation by Dipyridamole". This reference discusses the hemodynamic effect of intravenous infusions of adenosine and its affect on sympathetic activity. The reference concludes that adenosine administered by infusion of the range of 60 to 140 ug/kg/ minute to healthy conscious human subjects, lower diastolic blood pressure but raises heart rate, systolic blood pressure and levels of plasma norepinephrine.

5. Reference (5) by Hellmann et al. is entitled "Effect of Ethyl Adenosine on Myocardial Flow after Coronary Artery Occlusion". This reference discloses experiments performed in anesthetized dogs to determine the effect of an intracoronary bolus injection of ethyl adenosine-5-carboxylate hydrochloride on myocardial flow after artificial acute coronary artery occlusion, as determined by a radioactive microsphere technique. The authors alleged that the result of their study showed that ethyl adenosine-5-carboxylate significantly increased myocardial blood flow and decreased vascular resistance to both acutely ischemic, collateral dependent and normal areas of canine myocardium.

6. Reference (6) by Watt et al. is entitled "Adenosine Causes Transient Dilation of Coronary Arteries in Man". Applicants do not believe this reference is prior art

and cite it only out of an abundance of caution. This reference discloses tests performed in humans to determine the effects of adenosine on coronary blood flow and left ventricular function in man. The test were performed on patients who were shown to have no significant stenosis at coronary arteriography and no other obvious cardiovascular disease. The authors concluded that their tests allegedly showed adenosine increases coronary flow in man and that adenosine-induced changes in coronary blood flow are transient and might be usefully applied in the measurement of coronary flow reserve, as an alternative to atrial pacing or intravenous dipyridamole.

7. Reference (7) by Wilson et al. is entitled "Effects of Adenosine on Human Coronary Arterial Circulation". This reference is cited because applicants intend to rely on it in an amendment to be filed on a later date.

8. Reference (8) by Zijlstra et al. is entitled "Value and Limitations of Intracoronary Adenosine for the Assessment of Coronary Flow Reserve". This reference is cited because applicants intend to rely on it in an amendment to be filed on a later date.

9. Reference (9) by Pantely et al. is entitled "Adenosine Renewed Interest in an Old Drug". This reference is cited because applicants intend to rely on it in an amendment to be filed at a later date.

10. Reference (10), U.S. Patent No. 4,880,783 to Mentzer et al., corresponds to PCT Application Publication No.WO-A-8802258, which was published April 7, 1988. This application was cited in the European Search Report issued for the present applications European counterpart. The patent is entitled "Use of Adenosine, Hypoxanthine and Ribose-Containing Solution for Improved Protection of the Heart During Surgery". The patent discloses a cardioplegia solution for reducing ischemic damage to the heart during operations and/or transplantation. The cardioplegia solution is disclosed as containing adenosine, hypoxanthine and ribose in addition to the electrolytes contained in standard cardioplegia solutions.

11. Reference (11) is a PCT application which was published March 26, 1987. It is entitled "Continuous Intravenous Infusion of Adenosine to Human Patients, A Unit Dosage Form of Adenosine and Use of Adenosine for the Manufacture of Medicaments". This application was cited in the European Search Report issued for the present applications European counterpart. The application discloses administering adenosine to human patients by continuous intravenous infusion at levels which the heart blocking action of adenosine is not detected, to modify the hemodynamic properties of the patient. Specific indications for use disclosed in the reference include the induction of controlled hypotension, control of hypertensive crisis, effecting preferential coronary vasodilation, increasing blood flow in a coronary artery graft, increasing cardiac output, reducing platelet loss during coronary bypass surgery and facilitation of the induction of cardioplegia.

12. Reference (12) is a PCT application published July 21, 1983. It is entitled "A Pharmaceutical Composition for Preventing and Treating Ischemic Cell Damage and Methods for the Use and Preparation Thereof". This application was cited in the European Search Report issued for the present applications European counterpart. The application discloses a pharmaceutical composition for preventing and treating ischemic cell damage. The composition is stated to contain a physiologically acceptable, water-soluble salt of phosphoenolpyruvic acid and a physiologically acceptable, water-soluble salt of adenosine-5-triphosphoric acid in a mutual ratio of from 5:1 to 1000:1, preferable from 10:1 to 500:1, calculated on a molar basis. A method of preventing and treating ischemic cell damage by administering said composition is also disclosed.

Identification of the above listed references in not to be construed as an admission by Applicants or Applicants' attorneys that such references are available as prior art against the subject application.

Applicants have also submitted herewith PTO Form 1449 listing the above cited references.

Applicants respectfully request that the Examiner review the foregoing references and that these be made of record in the file history of the subject application.

Respectfully submitted,

Date 2/9/91

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